49. (Once Amended) The [F(ab)] Fab fragments of claim 45, wherein said [F(ab)] Fab fragments are derived from polyvalent IgG(T).

REMARKS

Applicants have amended the specification to update the status of the parent U.S. patent application referred to in the specification. Applicants have also amended claims 40 to 49 and the title to recite "Fab" instead of "F(ab)" and "antivenom" instead of "antivenin." This Amendment is supported throughout the specification and the original claims.

Rejection of claims 40-49
under 35 U.S.C. § 103 (Item 18)

The Examiner rejected claims 40-49 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al., as evidenced by Stedman's Medical Dictionary. Specifically, the Examiner contends that it would have been obvious to one of ordinary skill in the art to utilize Sullivan et al.'s purified antivenom polyvalent antibodies against venom of the Crotalus genus to produce antivenom compositions consisting of Fab fragments. The Examiner asserts that one of ordinary skill in the art would have been motivated to combine these references because Coulter et al. teaches a method of producing antivenom Fab fragments, and Smith et al. teaches the advantages of Fab fragments for the neutralization and clearance of toxic substances in therapeutic applications. Paper No. 21 at paragraph bridging pages 3 and 4.

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Applicants respectfully traverse this rejection. The Examiner concedes that the primary reference, Sullivan et al., does not teach an Fab containing antivenom. Id. at page 3, lines 12-13. The Examiner asserts that the Coulter et al. reference provides this teaching because it teaches a composition of Fab fragments against textilotoxin, and Stedman's Medical Dictionary defines antivenom as "an antitoxin specific for an animal or insect toxin." Id. at page 3, lines 14-19. Thus, the Examiner concludes that Coulter et al. teach antivenom Fab fragments. Id. at page 3, lines 19-20.

The Examiner contends that Stedman's Medical Dictionary defines antivenom as "an antitoxin specific for an animal or insect toxin." Paper No. 21 at page 3, lines 17-19 (emphasis added). However, Stedman's Medical Dictionary actually defines antivenom as "an antitoxin specific for an animal or insect venom." Stedman's Medical Dictionary at page 94. As shown by the enclosed definition, snake venom comprises many different toxins. Dorland's Illustrated Medical Dictionary, 1449 (26th ed. 1981). Crotalid Snake Venoms comprise 20 different compounds. Russell at Ch. 6, page 168. In some Crotalid venoms, there are as many as 100 protein fractions, of which at least 25 are enzymes. In less than 20 of the compounds, however, are the definitive pharmacologic activities known.

Chemically, snake venoms consist of proteases, phospholipases, hyaluronidase, collagenase, acetylcholinesterase, L-amino acid oxidase, hydrolases, nucleotidases, glycoproteins, lipids, metalloproteins and free amino acids. Pharmacologic activities include coagulant, anticoagulant, neurotoxic and other actions. Some of the more important reactions in humans are autopharmacologic, or the result of synergisms not

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provoked by a single venom fraction or antigen. Since the Coulter et al. reference teaches a composition of Fab fragments against textilotoxin, a single snake toxin, it does not teach an antivenom.

To further clarify Applicants' claimed invention, Applicants have amended claims 40 and 45 to specify that the venom comprises more than one toxin. Accordingly, Applicants respectfully request withdrawal of this rejection.

Not only was there no suggestion to combine the references as the Examiner has suggested prior to Applicants' invention, there was no reasonable expectation of success. Cleavage of an IgG molecule with papain results in separate Fab fragments and an Fc fragment. In contrast, cleavage with pepsin results in a single Fab'_2 fragment and a smaller Fc fragment. A single Fab'_2 fragment comprises the two Fab fragments as well as the portion of the heavy chains connected by a disulfide bond. Thus, each Fab has its own, single antigen binding site, and the Fab'_2 fragment has two antigen binding sites.

Since the Fab'_2 fragment contains two antigen binding sites, it may precipitate the antigen it binds. Stewart Sell, Basic Immunological: Immune Mechanism in Health and Disease 89, Fig. 6-3 (1987). In contrast, although an Fab fragment can bind an antigen, it cannot precipitate the antigen because it has only one antigen binding site. Id. Furthermore, an Fab-venom protein complex has a molecular weight that is greater than the molecular weight filtration limit of the kidney--typically 60 kd. Sullivan Declaration at sentence bridging pages 3 and 4. Therefore, Fab would not precipitate the venom protein, and the Fab-venom protein complex would remain in solution.

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Fab also has a much shorter half-life than venom protein. Indeed, Fab fragments require only 24 to 26 hours to be totally eliminated, whereas venom proteins require weeks for elimination. Sullivan Declaration at page 3, lines 24-26. For example, Ownby et al., Southern Medical Journal (August 10, 1996), detected Crotalidae snake venom in a patient forty-six days after envenomation.

Fab's inability to precipitate venom proteins and its short half-life led those of ordinary skill in the art to believe that Fab would not be effective in treating envenomation. Indeed, those of ordinary skill in the art actually believed that Fab would be harmful. Although Fab might bind venom proteins quickly, the Fab cannot precipitate the venom proteins. Therefore, the Fab-venom protein complex would remain in solution. Since Fab has a large volume of distribution, those of ordinary skill in the art believed that the Fab might actually introduce the venom proteins into other areas of the body then they were originally located. Sullivan Declaration at ¶ 5.

Furthermore, since Fab has a much shorter elimination period than venom proteins, and since free Fab was eliminated more quickly than venom protein, the bound Fab would unbind from the venom proteins to equilibrate. Thus, those of ordinary skilled in the art believed that Fab would also prolong the presence of the venom proteins in the body. Sullivan Declaration at ¶ 7.

Accordingly, prior to Applicants' invention, not only had no one successfully used an antivenom comprising Fab fragments, no one had even tried such an Fab composition. This is despite the fact that antivenoms comprising intact antibodies have been available since at least 1947, and antivenoms comprising Fab_2 fragments have

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been available since at least 1969. Smith Declaration at page 2, third full paragraph. Although those of ordinary skill in the art not only used intact immunoglobulins in antivenom compositions, but also digested these intact immunoglobulins to yield Fab_2 fragments, they went no further because of the expected disadvantages of Fab fragments.

Indeed, one of ordinary skill in the art cited these very concerns for antitoxin Fab therapy. Balthasar et al. studied the effect of antidigoxin Fab fragments for minimizing drug toxicity. Antidigoxin Fab fragments are the very fragments utilized by Smith et al., the reference the Examiner relies upon as allegedly providing the motivation to combine the cited references.

Balthasar et al. conclude,

> "there are, however, several concerns which must be addressed before the implementation of this type of therapy. First, the alteration of drug distribution which accompanies antibody drug complexation may result in a **potentiation of drug toxicities** or the development of **new drug toxicities** in certain cases . . . . The risk of **redistributing systemic toxicity**, rather than minimizing systemic toxicity, should be appreciated as a potential outcome of the proposed approach."

Balthasar et al. at page 738, paragraph bridging cols. 1 and 2 (emphasis added).

The Examiner dismisses Balthasar et al. on the ground that Balthasar et al. referred to alpha-amatoxin. Paper No. 21 at page 5, last full sentence. However, as Applicants have noted above, Balthasar et al. concerns digoxin, the same toxin as utilized by Smith et al., the reference the Examiner relies upon as allegedly suggesting combining these cited references. Furthermore, although Balthasar et al. cite Faulstich

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et al., which concerns alpha-amatoxin, Balthasar et al. discuss this reference in the context of drug-binding Fab fragments for the treatment of drug toxicity. Thus, Balthasar et al. believed that the results and teachings of Faulstich et al. were relevant and generalizable to drug toxicity in general.

The Examiner dismisses the Smith and Sullivan Declarations on the ground that they allegedly ignore that Coulter et al. teach that Fab antivenom can neutralize snake venom toxin. Id. at page 7, lines 8-10. Applicants respectfully disagree with this characterization. The Smith Declaration contains results showing that Fab antivenom was as effective as Fab_2 antivenom at a much lower dosage. Smith Declaration at page 5. In contrast, Coulter et al. teach a 20 to 30 percent loss of activities for Fab fragments. Thus, the results presented in the Smith Declaration show the unexpected results of the present invention, which are superior to Coulter et al.'s results.

The Examiner also dismisses the Smith and Sullivan Declarations on the basis of teachings contained in Sullivan (1986). However, the present application is entitled to a filing date of October 9, **1984**. Thus, Sullivan (1986) is not available as prior art to establish a reasonable expectation of success.

The Examiner dismisses Applicants' evidence of long felt but unmet need, as exemplified by the FDA's designation of the first purified Fab antivenom as an orphan drug, on the ground that the orphan drug is an ovine Fab. Paper No. 21 at page 7, lines 24-27. However, Smith et al., the reference the Examiner relies upon as providing the suggestion to combine the cited references, also involves an ovine preparation.

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Furthermore, Sorkine et al. state that there was no difference in the efficacy of ovine and equine Fab antivenom. Sorkine et al. at abstract.

Applicants respectfully submit that the Examiner cannot rely upon Smith et al., which used an ovine preparation, while rejecting Applicants' evidence of long felt but unmet need based upon another ovine preparation. If the Examiner persists in dismissing this evidence on this ground, Applicants respectfully request the Examiner to explain why Smith et al.'s ovine data is relevant, but Applicants' ovine data is not.

Finally, the Examiner dismisses the clinical results in the Smith Declaration on the grounds that the specification does not utilize the specific Fab antivenom composition utilized in that clinical study. Id. at sentence bridging pages 7 and 8. Although the data in the Smith Declaration concerned an Fab antivenom composition directed to the venom of a species of a different genus of snake, these data are relevant to the present invention. This Fab composition is obtained in the same way as Applicants' Fab composition and is directed to the same goal, neutralizing snake venom toxins. If the Examiner continues to maintain that these data are not relevant to Applicants' invention, Applicants respectfully request that the Examiner provide reasons or evidence to support his assertion.

Rejection of claims 43, 44, 48, and 49 under 35 U.S.C. § 112, second paragraph (Item 20)

The Examiner rejected claims 43, 44, 48, and 49 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Specifically, the

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Examiner contends that the claims reciting polyvalent IgG(T) are duplicative of the claims reciting simply IgG(T).

Applicants respectfully traverse this rejection. The Examiner supports the assertion that these claims are duplicative by stating that "both claims read on the same product." Applicants respectfully submit that this is not a valid test for duplicative claims. Indeed, claims reading on the same product are common in the same patent. For instance, many patents have genus and species claims. By definition, both the genus and the species claims would read upon the species. Thus, Applicants respectfully request withdrawal of this rejection.

Rejection of claims 45-49
under 35 U.S.C. § 103 (Item 21)

The Examiner rejected claims 45-49 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. in view of Coulter et al. Specifically, the Examiner contends that Sullivan et al. teach antivenom polyvalent antibodies and that Coulter et al. teach a method for producing Fab fragments against textilotoxin. Paper No. 21 at page 8, lines 21, through page 9, line 20. The Examiner contends that Coulter et al. suggest combining these two references because they teach that "EIAs of higher sensitivity have been claimed when Fab enzyme is used instead of IgG enzyme." Paper No. 21 at page 9, lines 21-27.

Applicants respectfully traverse this rejection. As Applicants discussed in response to the previous obviousness rejection, Coulter et al. teach Fab against a single neurotoxin, not against a complex mixture of enzymes and other peptides, like

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venom. Thus, the alleged suggestion of Coulter et al. to use Fab, instead of whole IgG, would apply solely to individual toxins. Accordingly, there is no suggestion to prepare Fab to a **venom** of a species of the Crotalus genus, and Applicants respectfully request withdrawal of this rejection.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested, and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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